“MULTICOMPONENT CRYSTALLOGRAPHIC MODIFICATION APPROACH FOR SOLUBILITY ENHANCEMENT AND FORMULATION DEVELOPMENT OF POORLY WATER SOLUBLE DRUGS”

A synopsis submitted for consideration of registration to degree of

Doctor of Philosophy

(Pharmaceutics)

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(2019-2022)

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Research Proposal
(Synopsis)

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Title of research proposal:

MULTICOMPONENT CRYSTALLOGRAPHIC MODIFICATION APPROACH FOR SOLUBILITY ENHANCEMENT AND FORMULATION DEVELOPMENT OF POORLY WATER SOLUBLE DRUGS

❖ INTRODUCTION

In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds eventually appear into the market place. From all these biopharmaceutical properties, solubility remains an important issue with drugs often discarded during commercial production due to their low solubility. Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. Multiple approaches have been carried for improving the aqueous solubility of drugs including micronisation, salt formation, emulsification, solubilisations using co-solvents and the use of polymer drug vehicles for delivery of poorly soluble drugs. Cocrystals are defined in a number of ways a restrictive definition utilised by Aakeroand Salmonyis that cocrystals are structurally homogeneous crystalline materials containing two or more components present in definite stoichiometric amounts. The cocrystal components are discrete neutral molecular reactants which are solids at ambient temperature. Based on this definition of cocrystals, a pharmaceutical cocrystal means a cocrystal with one of the cocrystal components as an Active Pharmaceutical Ingredient (API) and the other components are called coformers.From the definition, it is clearly shown that an API hydrate is not a cocrystal, however a solid-state API hydrate can cocrystallise with a solid conformer to form a cocrystal.[1]

- **Crystal engineering and supramolecular chemistry in cocrystal formation**

The term supramolecular synthon is frequently used in the research field of cocrystals. Desiraju (1995) defined cocrystal as structural units within supramolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interactions. Supramolecular synthons are spatial arrangements of intermolecular interactions and the overall goal of crystal engineering is therefore to recognise and design synthons that are robust enough to be interchanged between network structures. This ensures generality ultimately leading to the predictability of one-, two- and

three-dimensional patterns formed by intermolecular interactions. Pharmaceutically considerable cocrystal formers that are able to cocrystallise with dugs include.1

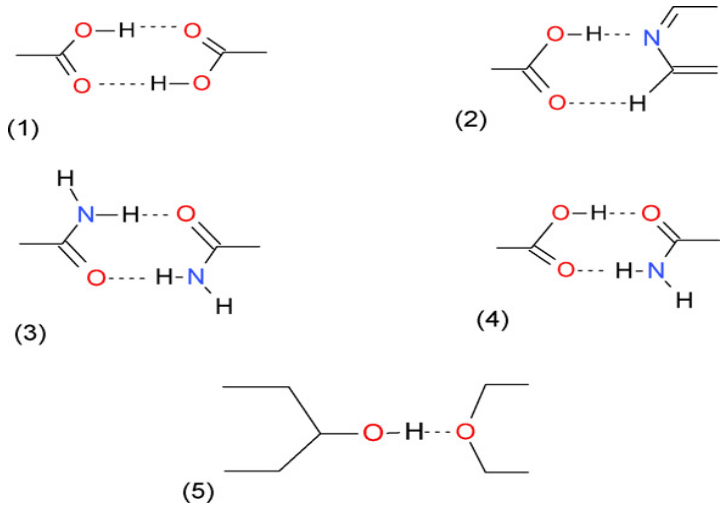

Fig. 1. Typical hydrogen bonds utilised in crystal engineerin

- **Cocrystal Preparation Methods**

Solid Based Methods	Solvent Based Methods
Neat grinding (Cogrinding) Holt melt extrusion Twin screw extrusion	**Solvent drop grinding** Antisolvent addition **Solvent evaporation/Solvent crystallization** Sonocrystallization Solvent mediated phase evaporation(SMPT) Super critical fluid technology

- **Solid Based Methods**

A) Neat grinding (Co-grinding)

There are two techniques for cocrystal preparation via grinding. The first one is neat grinding, that is also called dry grinding, consisting of mixing the stoichiometric cocrystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill. This method requires one or both reactants exhibiting significant vapour pressures in the solid state.1

B) Holt melt extrusion

Extrusion is a process that involves forcing a raw material or blend through die or orifice under set conditions such as temperature, pressure, rate of mixing and feed rate,for the purpose of producing a stable product of uniform shape and density.In this technique the API and(Cocrystal Former)CCF is mixed together and then feed into the Holt melt extruder, with different extruder screw configurations and different extruder barrel temperature profiles (at varying temperature and screw speeds/rpm) and are extruded for the specified period of time.[2]

C) Twin screw extrusion

Twin screw extrusion (TSE) as a scalable and green process for the preparation of cocrystals. Temperature and extent of mixing in the extruder were the primary process parameters that influenced extent of conversion to the cocrystal in neat TSE experiments. TSE provides highly efficient mixing and close material packing of components which in turn lead to improved surface contact between components thereby facilitating cocrystal formation without the use of solvents.2

- **Solvent Based Methods**

A) Solvent drop grinding

The second technique for cocrystal synthesis using solvent is liquid-assisted grinding (also referred to as kneading, solvent drop,wet cogrinding). Improvements in kinetics of cocrystal formation with grinding can be achieved by the addition of small amounts of an appropriate solvent. The improvements in kinetics might be rationalised by the additional degrees of orientational and conformational freedom open to molecules at the various interfaces as well as the enhancement of opportunities for molecular collisions. In addition, tiny cocrystal seeds may be envisaged to form within the solvent during the grinding process so that the rate of cocrystallisation can be increased. Besides increasing the cocrystallisation rate, the method of solvent-drop grinding (SDG) can control over the polymorphic outcome of cocrystallisation. The nature of solvents using in grinding may have a profound effect on the process of the mechanochemical reaction. The SDG method has been demonstrated to be a novel means of obtaining a particular caffeine–glutaric acid cocrystal polymorph.The choice of solvent used in grinding is important and one basic requirement is that it should be able to dissolve at least part of the original components. Comparing this method to the slow evaporation cocrystallisation method, little solvent is used in SDG, which therefore appears to be a cost-effective, environment friendly,and reliable method for the discovery of new cocrystals as well as for the preparation of existing cocrystals.1

B) Antisolvent addition

This is one of the methods for precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers(pH) and organic solvents.1

C) Solvent evaporation

Cocrystallisation by evaporation of stoichiometric solutions isbased on strategy 1 and itis the most important tool for cocrystal screening. In order to design successful cocrystal screening experiments,it is very important to consider reactant solubilities.

D) Sonocrystallization

Ultrasonic irradiation has been shown to have several effects on crystallization processes, including a decrease in the supersaturation and time necessary for nucleation. The only significant effect of ultrasound observed was a decrease in variation between results. Experiments with batch insonation showed that the flow pattern and insonation time influence the number of crystals produced, but insonation times were limited by the temperature increase due to insonation. Batch crystallization experiments with lactose showed that nucleation could be induced by ultrasound at high supersaturation ratios. Crystals observed had a rhomboid shape, which is due to the high supersaturation used. Increasing supersaturation ratios increased both the number of crystals produced and their average size. Increasing the insonation time also increases the number of crystals produced and their average size.[3]

E) Solvent mediated phase evaporation(SMPT)

SMPT is an effective and convenient co-crystal screening method in the pharmaceutical industry to improve screening efficiency, particularly when utilizing co-crystal formers (CCF) that exist as solids under ambient conditions. The approach is based on the thermodynamic understanding of the physical stability of hydrates/solvates, a sub-group of co-crystals where the CCF exist in the liquid or gas state under ambient conditions.[4]

F) Super critical fluid technology

The supercritical fluid technology offers established organic chemical free processes that can be implemented by the pharmaceutical industry for the successful development of their products. In addition to the traditional methods of producing cocrystals, the use of supercritical fluids (SCFs) offers a new platform for the cocrystallization of APIs, bringing additional advantages compared to the classical cocrystal production methods. The potential of SCFs as new media for the cocrystallization of APIs has been addressed recently. It has been shown that different supercritical fluid techniques can be used to produce cocrystals by taking advantage of different supercritical fluid properties (solvent, anti-solvent or atomization enhancement), bringing additional advantages compared to the classic.[5]

❖ HYPOTHESIS OF RESEARCH TOPIC:-

Pharmaceutical cocrystals represent a strategic opportunity for the optimization of key physicochemical properties of an API whilst retaining its molecular structure, and hence its physiological activity as there are no making or breaking of the API's covalent bonds. Significant physicochemical properties of an API such as its solubility, bioavailability, processability features can be considerably improved upon cocrystallization, thus allowing for optimal drug formulation.

❖ OBJECTIVE OF RESEARCH WORK :-

The objective for the proposed research are as follows

1) To study coformer and drugs physicochemical properties

2) To screen coformer for solubility improvement of drug

3) To use Hansen solubility parameter as a prediction tool for formation of cocrystal

4) To prepare cocrystal using robust and scalable methods

4) To study cocrystal physicochemical properties

6) To formulate and optimize the cocrystal tablet.

7) To perform stability study of optimum batch

❖ USEFULNESS OF RESEARCH WORK

1) Improvement in drug's solubility and ultimately bioavailability

2) Provide optimized and novel approach for drug formulation.

3) Stability problem of API can be minimize.

❖ REVIEW OF LITERATURE

▪ Research and Review Articles

- **Trask et. al. (20006),** The crystal form adopted by the respiratory drug theophylline was modified using a crystal engineering strategy in order to search for a solid material with improved physical stability. Cocrystals, also referred to as crystalline molecular complexes, were prepared with theophylline and one of several dicarboxylic acids. Different cocrystals of theophylline were reported, one each with oxalic, malonic, maleic and glutaric acids. Crystal structures were obtained for each cocrystal material, allowing an examination of the hydrogen bonding and crystal packing features. The cocrystal design scheme was partly based upon a series of recently reported cocrystals of the molecular analogue, caffeine, and comparisons in packing features are drawn between the two cocrystal series. The theophylline cocrystals were subjected to relative humidity challenges in order to assess their stability in relation to crystalline theophylline anhydrate and the equivalent caffeine cocrystals. None of the cocrystals in this study converted into a hydrated cocrystal upon storage at high relative humidity. Furthermore, the theophylline:oxalic acid cocrystal demonstrated superior humidity stability to theophylline anhydrate under the conditions examined, while the other cocrystals appeared to offer comparable stability to that of theophylline anhydrate. The results demonstrate the feasibility of pharmaceutical cocrystal design based upon the crystallization preferences of a molecular analogue, and furthermore showthat avoidance of hydrate formation and improvement in physical stability is possible via pharmaceutical.[6]
- **. Yadav A. V. et. al. (2010),** studied the effect of cocrystallization with different cocrystal farmers on physicochemical properties of mefloquine hydrochloride. The cocrystals were prepared by solution crystallization method using mefloquine hydrochloride and different cocrystal formers (citric acid, benzoic acid, oxalic acid, saccharin, salicylic acid, and succinic acid) at a ratio of 1:1, 1:0.5 mMol ratio, using ethanol as solvent. The cocrystals showed enhanced solubility and dissolution rate. The cocrystais were found to be stable over the period of 6 months confirmed from stability studies. They resist the conversion of anhydrous form of drug into its hydrate, which is responsible for the drugs less solubility and dissolution rate.[7]
- **Remenar J. F. et.al (2003),** prepared cocrystals of itraconazole which is extremely water-insoluble antifungal drug marketed in the amorphous form (Sporanox capsule) to achieve required oral bioavailability. Successful cocrystallization was resulted with fhmaric acid L-tartaric acid, succinic acid, D-tartaric acid, L-malic acid, DL-tartaric

acid using a High Throughput (HT) crystallization screen The discovery of stable cocrystals consisting of hydrogen-bonded trimers of two molecules of itraconazole and one molecule of a dicarboxyllic acid resulting in stable cocrystals.The solubility and dissolution properties of cocrystals were superior to the crystalline pure phase, thus presenting opportunities to increase bioavaiiability even in cases where stable.[8]

- **Basavoju S. et.al (2006),** investigation was the structural and pharmaceutical properties of Norfloxacin (a poorly soluble antibacterial drug), its cocrystal, and salts. Norfloxacin in the anhydrous form (form A) was cocrystallized with isonicotinamide, and organic salts were prepared with succinic acid, malonic acid, and maleic acid by solution evaporation, or crystallization from solution method in the cocrystal, isonicotinamide forms an amide dimer synthon and additional hydrogens of the amide group interact with the carboxylate group of norfioxacin molecules. The present study reported a new cocrystat and salts of norfioxacin with improved aqueous solubility, showed a 3-45 times increase in the solubility as compared to that of the starting material.[9]
- **Padreta L. et al. (2009),** studied to check the feasibility of supercritical fluid (SCF) technologies in the screening and design of coerystals. The cocrystal formation tendencies in different SCF techniques, focusing on distinct supercritical fluid properties-solvent, anti-solvent and atomization enhancer were found. The effect of processing parameters on the cocrystal formation behaviour and particle properties was studied. Indomethacin—saccharin (ND—SAC) cocrystal was used as model system. A 1:1 ratio of indomethacin (gamma form) and saccharin was used. The SCF techniques applied include the CSS technique (cocrystallization with supercritical solvent), the SAS technique (supercritical anti-solvent), and the AAS technique (atomization and anti- solvent). The pure IND—SAC cocrystals were obtained from SAS and AAS processes. potential of SCF for the screening, design, and development of eocrystals in a single-step, offering advantages: over classical pharmaceutical techniques, such as extended control of the particle morphology and the size distribution. 5
- **Hickey M. B. et. al. (2007),** studied the carbamazepine: saccharin cocrystal in terms of suitability for multi-gram scale-up, propensity for crystal polymorphism, goal of physical stability, in vitro dissolution and oral bioavailability, with the comparing with marketed form of carbamazepine (Tegretol). Carbanizepine an important anti-epileptic agent, an example of a water-insoluble drug used in high dose (>100 mg/day) for therapeutic effect. It poses multiple challenges for oral drug delivery,

including a dissolution-limited bioavailabi!ity, narrow therapeutic window, autoinduction of metabolism. Preparation of Cocrystal was achieved on a 30g scale with a conventional cooling crystallization process from alcohol without seeding. The benefits of using carbamazepine:saccharin cocrystal include (i) relative lack of polymorphism, (ii)equivalent physical and chemical stability to anhydrous polymorph in the marketed product (iii) favorable dissolution properties and suspension stability, and (iv) comparable oral absorption profile in dogs compared with the commercial immediate release product (Tegretol).[10]

- **Mohammad M.S. et. al (2011)** investigated whether the miscibility of a drug and coformer, as predicted by Hansen solubility parameters (HSPs), can indicate cocrystal formation and guide cocrystals screening. Using the group contribution method to calculate partial solubility parameters and Van Krevelen-Hoftyzer, Bagley and (Greenhalgh approaches to predict miscibility, 21 of 33 coformers were tested predicted and confirmed to be miscible with indomethacin. Out of these miscible systems, four (4) coformers formed cocrystals with indomethacin, including two (2) that were previously unknown. Thus, the miscibility between cocrystal components appears to be necessary for cocrystal formation. Thus two new coerystals of indomethacin were discovered in this study.[11]
- **Masuda T. et. al (2012),** Cocrystal screenin and the presence of amorphous acyclovir was conducted with various pharmaceutical excipients, with the use of the solution-crystallization method and liquid-assisted cogrinding. Low bioavailability of acyclovir is related to its poor solubility in aqueous media. Acyclovir has absorption problems because-of its low solubility. Thus influence the oral bioavailability, which attains just 15-30%. Acyclovir exists in a hydrated form with a ratio of acyclovir to water molecules in the crystal structure. In the present study, novel cocrystals of acyclovir were formed by interactions between the drug and the pharmaceutical excipient 1-tartaric acid and characterized using PXRD, TG/DTA, ET-1R, HPLC. This article describes the pharmaceutical characterization of the acyciovir—tartaric acid cocrystal (ACV—TA cocrystal. The saturated solubility of the cocrystals and the intransic dissolution rate of the cocrystals were considerably higher than that of acyclovir.[12]
- **Tsutsumi S. et.al. (2011**), studied the potential of salts and cocrystals of miconazole to improve its physicochemical properties by the crystallization screening, Miconazole freebase shows very low solubility in water (less than lpsg/mL). In 20 ml, toluene at 50°C, and 100 mM 1,4-dioxane solutions of maleic acid, furnaric acid, and

succinic acid were added to prepare molar ratios of 1:1, 2:1, and 2:1 miconazole/acid mixtures, respectively Novel miconazole crystal forms (maleate, hemifumarate, and hemisuccinate) were characterized X-ray diffraction analysis revealed that maleate is a salt, whereas hemisuccinate and hemifumarate are cocrystals. Intrinsic dissolution tests showed that both the salt and cocrystal forms were with improved solubility. Hemisuccinate is a novel cocrystal form of miconazole with an improved dissolution rate and superior stability, making it a optimal alternative to nitrate.[13]

- **Goud et.al (2012),** screened furosemide, a BCS class IV drug, in cocrystallization experiments with pharmaceutically acceptable coformer molecules to discover cocrystals of improved physicochemical properties, that is high solubility and good stability. Eight new equimolar cocrystals of furosemide were obtained by liquid-drop grinding and slurry methods with (i) caffeine, (ii) urea, (iii) p-aminobenzoic acid, (iv) acetamide, (v) nicotinamide, (vi) isonicotinamide, (vii) adenine, and (viii) cytosine The solubility order for the stable forms is fiirosemide>cytosine>fiirosemide>adenine>furoseinide—>caffeine, and their solubilities are approximately 11-, 7-, and 6-fold higher than furosemide. The dissolution rates of furosernide cocrystals were about two times faster than the other drug. Three (3) novel furosemide compounds of higher solubility and good phase stability were identified in a solid form screen.[14]
- **Bhatt et.al. (2009),** studied Cocrystal forming abilities of the two anti-HIV drugs lamiviidine and zidovudine were studied. A study of cocrystallization was carried out on Lamivudine with five cocrystals formers with saccharin, quinolinone, 3,5-dinitrosalicylicacid), 2,4,6-Triaminopyrimidine and Zidovudine using solution crystallization and grinding with solvent-drop addition was used as screening methods. Both lamivudine and zidovudine contain multiple hydrogen bond donor and acceptor groups. These groups can be used for designing cocrystals of the two APIs. From the cocrystals obtained, the retrosynthetic approach for the design of API cocrystals was successfully proven.[15]
- **Viertelhaus et.al (2009),** reported the synthesis, crystal structures, and basic physicochemical properties of six cocrystals of piracetam. Cocrystals of piracetam with U- tartaric acid, with citric acid in a 1:1 and 3:2 ratio, with racemic mandelic acid, and with L-mandelic acid, as well as a piracetam-citric acid ethanol solvate were found in a focused screening approach using either solvent-drop grinding, solution evaporation, or crystallization from solution. The piracetam-L-tartaric acid

ocrystal shows improved hygroscopic properties in contrast to pure piracetam form 111, for which deliquescence was observed at 95% relative humidity.[16]

- **Childs S.L. et.al (2007).** A crystal engineering method was used to investigate cocrystallization of piroxicam with carboxylic acids as a coformer. Forming coerystals of piroxicam can potentially result in solid forms with increased bioavailability. A total of fifty unique cocrystals containing piroxicam and carboxylic acid were identified during screening. Each of the 23 coformers tested formed at least one cocrystal with piroxicam. Raman data for the piroxicam cocrystals can be interpreted into three distinct groups based on spectral similarity. These groups are differentiated by the piroxicam tautomer present in the cocrystal and the presence or absence of a strong hydrogen bond donor interacting with piroxicam' s amide carbonyl group. X-ray powder diffraction data exposed six isostructural piroxicam cocrystals.[17]
- **Nangia A. et.al (2011).** The present investigates Hydrogen-bond motifs for the supramolecular synthones of sulfonamidepyridine-N-oxide complexes were derived from the analysis of cocrystal structures of aryl sulfonamides and pyridine-N-oxides. The sulfonamide NH donor persistently interacts with the N-oxide acceptor via a N-H 3330 hydrogen bond, though the exact geometry of the motif, such as discrete (D), infinite chain C(4), cyclic motifs R4 2(8) or R2 2(4), varies from structure to structure.Surprisingly, the two-point R2 2(8) cyclic motif of N1-13 330 and Cl-fl 3 30 hydrogen bonds, analogous to the heterosynthon in carboxaniide_pyridine-N-oxide cocrystals, was not observed in sulfonamide N-oxide cocrystals. The utility of this model study is demonstrated by making cocrystals of Furosemide with 4,40-bipyridine-N,N0-dioxide and isonicotinamide-N-oxide.[18]

➢ PATENT SEARCH

- **Zegarac W02008080362A1(2007). et.al.** The present invention relates to pharmaceutical cocrystals of sildenafil. Sildenafil citrate, molecule with moderate water solubility, has been commercially developed and marketed by Pfizer, under trademark Viagra®. It has been observed that sildenafil in a pharmaceutical cocrystal form could improve solubility of the API under acidic conditions, which could be particularly advantageous for its orally administrable formulation. Sildenafil cocrystals were prepared with acetylsalicylic acid (1:1 molar ratio) by slurry or under reflux conditions. An intrinsic dissolution study, in simulated gastric body fluid (pH 1.2) shows that the sildenafil: acetylsalicylic acid cocrystal exhibits a greater intrinsic dissolution rate (IDR) over sildenafil citrate under the same conditions.[19]

- **Devarakonda US20090054455A1 (2009) et.al.** The present invention relates to preparation of Aripiprazole cocrystals with funiaric acid, nicotinic acid, benzoic acid, succinic acid, and L-tartaric acid and processes for cocrystal preparation by reacting approximately equimolar amounts (0.5 mMol) using solvent evaporation and anti-solvent addition method utilizing DM50 and DMF as solvents. Aripiprazole is a psychotropic drug useful for the treatment of schizophrenia. It has a very low solubility in aqueous media (being practically insoluble) and therefore is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally, for example in tablet form.A successful formation of AripiprazoleFumaric acid cocrystals was achieved. A new cocrystals phase Aripiprazole-Fumaric acid with improved solubility, bioavailability and stability was obtained.[20]
- **Nangia W02011036676A2 (2011) et,al**. The present invention relates to preparation of Temozolomide cocrystals with oxalic acid, anthranilic acid, salicylic acid, succinic acid, and tartaric acid and processes for cocrystal preparation by solvent drop grinding and further recrystallizing it from solvents by reacting approximately.equimolar amounts (1 :O.5mMol) usingsolvent evaporation method utilizing acetone as solvent. Temozolamide rapidly decomposes in aqueous medium and in high relative humidity, with change in its colour from pure white to light pink to light tan. By cocrystallization with the carboxylic acids stability, solubility and improved dissolution rate of temozolomide was successfully modified. Along with improved stability in aqueous medium, the dissolution rate was also improved.[21]

- **Evanthia Dova US20090270352 (2009**) **et.al.** The present invention derived a newer crystalline form of Tenofovir disoproxil fumarate (Tenofovir DF), designated cocrystal TOFA 2:1, methods for the preparation thereof and its use in pharmaceutical applications, in particular in anti-WV medicaments. Tenofovir disoproxil fortunate (DF) is a nucleotide reverse transcriptase inhibitor approved in the United States for the treatment of HIV-1 infection alone or in combination with other antiretroviral agents. In Tenofovir DF, conversion of its crystalline form into the other form when put under stress, such as increased temperature and/or humidity leads to reduced stability Cocrystallization of Tenofovir DF was attempted with fumaric acid by solvent evaporation and anti-solvent addition method using 2,2,2 - trifluoroethanol, acetone, dichioromethane, nitromethane or water as solvents. A Tenofovir DF-Fumaric acid (TDPA 2:1) cocrystal was obtained and is more stable and is less hygroscopic than the presently known crystalline form of tenofovir DF.[22]

❖ **PLAN OF WORK :-**

Time duration	Plan of work
July 2019-December 2019	**A) Literature screening with respect to problem selected** a) Literature survey with respect to selected problem from reputed research journals and patents b) Selection of drug candidate (API) c) Selection of cocrystal formers (CCFs) d) Selection of solvent
January 2020 – June 2020	**B) Physicochemical characterization of API and CCFs** a) Melting point b) FTIR c) DSC d) Saturated solubility determination e) Flow properties
July 2020 - December 2020	**C) Analytical method development** **D) Preparation of cocrystals**
January 2021 – June 2021	**E) Characterization of cocrystals** a) Melting point b) FTIR c) DSC d) XRD **F) Preformulation study of cocrystals** a) Compressibility determination b) Drug content analysis c) Solubility determination d) Dissolution determination e) Flow properties
July 2021 - December 2021	**G) Development and Evaluation of Formulation** a) Selection of dosage form b) Preparation of formula c) Preliminary formulation c) Optimization of formula d) Preparation of formulation e) Evaluation of formulation f) Stability study
January 2022 – June 2022	Research Publications and Thesis writing.

❖ EXPECTED OUTCOMES :-

Theoretically calculated solubility parameter of drug must match with practically determined solubility parameter in given solvent.

Increase solubility of drug

Increase dissolution of drug

Increase bioavailability

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